Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a four year follow up study in men

Jukka T Salonen, Kristiina Nyyssönen, Tomi-Pekka Tuomainen, Pekka H Mäenpää, Heikki Korpela, George A Kaplan, John Lynch, Susan P Helmrich, Riitta Salonen

Abstract

***Objective*—To investigate whether low vitamin E status is a risk factor for incident non-insulin dependent diabetes mellitus.**

***Design*—Population based follow up study with diabetes assessed at baseline and at four years.**

***Setting*—Eastern Finland.**

***Subjects*—Random sample of 944 men aged 42-60 who had no diabetes at the baseline examination.**

***Intervention*—Oral glucose tolerance test at four year follow up.**

***Main outcome measures*—A man was defined diabetic if he had either (*a*) a fasting blood glucose concentration ≥6·7 mmol/l, or (*b*) a blood glucose concentration ≥10·0 mmol/l two hours after a glucose load, or (*c*) a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment.**

***Results*—45 men developed diabetes during the follow up period. In a multivariate logistic regression model including the strongest predictors of diabetes, a low lipid standardised plasma vitamin E (below median) concentration was associated with a 3·9-fold (95% confidence interval 1·8-fold to 8·6-fold) risk of incident diabetes. A decrement of 1 μmol/l of uncategorised unstandardised vitamin E concentration was associated with an increment of 22% in the risk of diabetes when allowing for the strongest other risk factors as well as serum low density lipoprotein cholesterol and triglyceride concentrations.**

***Conclusions*—There was a strong independent association between low vitamin E status before follow up and an excess risk of diabetes at four years. This supports the theory that free radical stress has a role in the causation of non-insulin dependent diabetes mellitus.**

Research Institute of Public Health, University of Kuopio, PO Box 1627, 70211 Kuopio, Finland
Jukka T Salonen, *academy professor*
Kristiina Nyyssönen, *research associate*
Tomi-Pekka Tuomainen, *research associate*
Riitta Salonen, *research scientist*

Department of Biochemistry and Biotechnology, University of Kuopio
Pekka H Mäenpää, *professor*

Department of Community Health and General Practice, University of Kuopio
Heikki Korpela, *assistant professor*

Human Population Laboratory, California Department of Health Services, Berkeley, California, USA
George A Kaplan, *chief*
John Lynch, *research scientist*
Susan P Helmrich, *research scientist*

Correspondence to:
Professor Salonen.

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Introduction

Free radical mechanisms have been implicated in the pathogenesis of tissue damage in diabetes.[1-5] Various sources of free radicals may modulate oxidative stress in diabetes, including non-enzymatic glycosylation of proteins and monosaccharide auto-oxidation, polyol pathway activity, indirect production of free radicals through cell damage from other causes, and reduced antioxidant reserves.[3]

There are few data on the role of oxidative stress in the causation of diabetes, though some workers have suggested a role for free radicals and lipid peroxidation.[1] It has been speculated that as pancreatic islet cells have low antioxidative enzyme activities they might be sensitive to free radical injury.[2 6] Diabetes can be induced in animals by free radicals producing substances such as catalytic iron, alloxan, and streptozocin, and free radical scavengers are effective in preventing diabetes in animal models.[1 2 6-10]

In humans the evidence concerning the role of free radicals and antioxidants in diabetes is very limited. Increased lipid peroxidation has been detected in diabetic patients by several different methods.[11-14] In a small randomised trial in non-insulin dependent diabetic and healthy subjects supplementation with vitamin E reduced oxidative stress and improved insulin action.[15 16] There is, however, no previous prospective population study of the role of either free radical stress or antioxidants with regard to the incidence of diabetes. We tested the hypothesis that the incidence of non-insulin dependent diabetes mellitus is increased at low concentrations of plasma vitamin E.

Subjects and methods

The Kuopio ischaemic heart disease risk factor study is a population study of the role of lipid peroxidation, pro-oxidative minerals, and antioxidants in atherosclerosis, coronary heart disease, and diabetes.[17] Baseline examinations were conducted between March 1984 and December 1989. The study sample comprised 3235 men in eastern Finland aged 42, 48, 54, or 60 years at the baseline examination. Of these, 2682 (82·9%) eligible men participated. No appreciable sociodemographic differences have been found between participants and non-participants.[18]

Men who participated in the baseline examinations during September 1986 to December 1989 and had ultrasonography of the carotid arteries were invited for re-examination four years later. Of the 1229 eligible men who were invited, 1038 participated, 107 refused, and 84 could not participate. Forty five subjects had diabetes at the baseline examination, as defined by a fasting blood glucose concentration ≥6·7 mmol/l or diagnosed diabetes with dietary, oral, or insulin treatment. As this study was concerned with the risk of the first manifestation of diabetes, these subjects were excluded from analysis. Plasma vitamin E, serum total cholesterol, or serum triglyceride concentrations were missing for 49 other subjects, so that data were available for 944 men.

NON-INSULIN DEPENDENT DIABETES MELLITUS STATUS

The examination protocol and measurements were as detailed elsewhere.[17-19] An oral glucose tolerance test with 75 g glucose was performed at the four year follow up visit. Incident diabetes was defined by means of the WHO criteria for diabetes,[20] complemented by a clinical diagnosis that had led to treatment, which had thus influenced the glucose concentration. A man was defined diabetic at the four year follow up if he had either (*a*) a fasting blood glucose concentration ≥6·7 mmol/l, or (*b*) a blood glucose concentration ≥10·0 mmol/l two hours after a glucose load, or (*c*) a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment. Forty five subjects became diabetic during the four years of follow up (table I).

OTHER MEASUREMENTS

Vitamin E concentration was measured in deep frozen (−80°C) heparinised plasma as α tocopherol by high performance liquid chromatography.[21] The freezing time was less than a year. For serum low density lipoprotein cholesterol analysis fresh serum was centrifuged for 16 hours at 115 000 *g* at 10°C (TGA-65 ultracentrifuge, Kontron Instruments, Italy), as described.[19] Plasma cholesterol concentrations were determined by enzymatic colorimetry

(CHOD.PAP, Boehringer Mannheim, Germany). Serum triglyceride and fructosamine concentrations were measured in frozen samples by an autoanalyser (Kone Specific, Kone Inc, Finland) with the use of reagents from Boehringer Mannheim. Serum fatty acid concentrations were measured by gas chromatography (Hewlett Packard 5890 series II with a flame ionisation detector, Avondale, Philadelphia). An NB-351 capillary column was used (HNU-Nordion, Finland).

The number of cigarettes, cigars, and pipefuls of tobacco smoked daily and the years of regular smoking were recorded with a self administered questionnaire, which was checked by an interviewer. Reinterviews for a medical history were conducted by a physician. A family history of diabetes was recorded as positive if either the biological father, mother, sister, or brother of the subject had a history of diabetes. Consumption of alcohol in the previous 12 months was assessed by the quantity-frequency method with the Nordic alcohol consumption inventory, which contains 15 items.[22] Socioeconomic status was measured with a summary index that combined income, education, occupation, occupational prestige, material standard of living, and housing conditions.[23]

STATISTICAL METHODS

The association of baseline plasma vitamin E concentration and other risk factors for diabetes with the risk of incident diabetes was estimated and tested for statistical significance by the SPSS software for multivariate logistic regression analysis.[24] Other risk factors for incident diabetes and thus potential confounders of the relation between vitamin E status and diabetes were explored by step up logistic regression analysis. The strongest predictors were then included as covariates in a fixed logistic model jointly with lipid standardised vitamin E concentration. The purpose of also including baseline blood glucose and serum fructosamine concentrations in the model was to control for any association between baseline vitamin E value and indicators of early diabetes. Baseline serum insulin concentration was also tested for entry but did not have any additional predictive value.

To separate the effect of vitamin E from that of serum lipids, lipid standardised vitamin E concentration was used in the statistical analysis. The lipid standardised vitamin E concentration was computed as the ratio of the measured plasma vitamin E concentration to the vitamin E concentration predicted by a linear regression equation based on serum total cholesterol and serum triglyceride concentrations. The alternative approach, to enter these three variables jointly into a model, was also used to confirm the results. To ensure maximal statistical power the lipid standardised vitamin E concentration was dichotomised by using the median as a cut off point.

TABLE I—*Distribution of diagnostic criteria in 45 subjects who became diabetic during four year follow up*

	Fasting blood glucose ≥6·7 mmol/l		Fasting blood glucose <6·7 mmol/l		
	2 hour blood glucose ≥10·0 mmol/l	2 hour blood glucose <10·0 mmol/l	2 hour blood glucose ≥10·0 mmol/l	2 hour blood glucose <10·0 mmol/l	Total
Clinical diagnosis of diabetes	5	2	2	7	16
No clinical diagnosis of diabetes	12	2	15	0	29
Total	17	4	17	7	45

Results

The baseline characteristics of the study subjects are shown in table II. The mean plasma vitamin E concentration was comparatively low (19·4 μmol/l). The mean daily dietary intake of vitamin E was 9·9 mg (SD 4·3 mg; range 2·8-38·9 mg). For 566 (60%) subjects the daily intake was less than 10 mg, the recommended dietary allowance. Only 12 subjects (1·3%) had used vitamin E supplements in the seven days before the baseline examination.

Lipid standardised baseline plasma vitamin E concentration was 10% (P=0·001 for difference) lower among men who became diabetic during follow up than among those who did not develop incident diabetes (table II). The unstandardised plasma vitamin E concentration did not differ significantly between these two groups. Men who later developed diabetes also had a raised baseline body mass index (weight (kg)/height (m)^2), raised blood glucose and serum fructosamine concentrations, a higher ratio of saturated fatty acids to the sum of monounsaturated and polyunsaturated fatty acids, and a higher serum triglyceride concentration.

Lipid standardised plasma vitamin E concentration had only weak correlations with other potential risk factors for diabetes. It correlated inversely with cigarette smoking ($r=-0·143$; $P<0·001$) and the ratio of saturated to other fatty acids in serum ($r=-0·137$; $P\leq0·001$) and directly with socioeconomic status ($r=0·126$; $P\leq0·001$) and age ($r=0·115$; $P\leq0·001$). There were no strong intercorrelations among the variables that predicted the risk of diabetes.

In a multivariate logistic regression model including the strongest predictors of diabetes the baseline body mass index was the strongest predictor (table III). Other factors with significant associations with an excess risk of diabetes were a high ratio of saturated to other fatty acids in serum, low plasma vitamin E concentration, and high socioeconomic status. The number of cigarettes smoked daily and age had weak, non-significant associations with diabetes risk. A low lipid standardised vitamin E (below median)

TABLE II—*Baseline characteristics of subjects who developed diabetes during follow up and of those who did not*

Baseline characteristic	Incident diabetic subjects		Non-diabetic subjects		P value for difference in means	All subjects			
	Mean	SD	Mean	SD		Mean	SD	Minimum	Maximum
Plasma vitamin E (μmol/l)	18·9	6·3	19·4	5·2	0·662	19·4	5·2	6·5	54·9
Lipid standardised vitamin E	0·906	0·178	1·005	0·206	0·001	0·96	0·20	0·36	2·22
Dietary vitamin E intake (mg/d)	9·3	3·4	10·0	4·3	0·240	9·9	4·3	2·8	38·9
Serum total cholesterol (mmol/l)	5·74	1·05	5·76	0·99	0·901	5·76	1·00	2·60	10·09
Serum low density lipoprotein cholesterol (mmol/l)	3·75	0·96	3·87	0·93	0·422	3·86	0·93	0·82	8·46
Serum triglycerides (mmol/l)	2·12	1·34	1·37	0·79	0·001	1·41	0·84	0·25	7·84
Age (years)	52·1	6·1	51·9	6·7	0·888	52·0	6·7	42·0	61·3
Socioeconomic status (higher the score, lower the status)	9·3	4·6	10·3	4·5	0·160	10·3	4·5	0	21
Body mass index (kg/m^2)	30·0	4·3	26·5	3·2	<0·001	26·7	3·3	18·8	40·3
Cigarettes smoked daily	7·0	10·7	5·3	9·4	0·287	5·3	9·5	0	60
Blood glucose (mmol/l)	5·3	0·6	4·5	0·4	<0·001	4·6	0·5	3·2	6·5
Serum fructosamine (mmol/l)	258	24	246	25	0·002	246	25	132	386
Ratio of serum saturated fatty acids to sum of monoenes and polyenes	0·57	0·07	0·52	0·06	<0·001	0·52	0·06	0·15	0·77

TABLE III—*Relative risk of diabetes associated with low plasma vitamin E concentration and other risk factors*

Risk factor for diabetes	Relative risk	95% confidence interval	P value
Lipid standardised vitamin E below median (0·98)	3·90	1·76 to 8·61	0·0008
Age (years)	1·02	0·97 to 1·07	0·5401
Socioeconomic status	1·10	1·02 to 1·19	0·0122
Body mass index (kg/m²)	1·23	1·13 to 1·33	<0·0001
Cigarettes smoked daily	1·015	0·985 to 1·046	0·3274
Ratio of serum saturated fatty acids to sum of monoenes and polyenes	1·09	1·036 to 1·143	0·0007

Model $\chi^2=71·82$ (df=6); $P<0·0001$.

concentration was associated with a 3·9-fold (95% confidence interval 1·8-fold to 8·6-fold; P=0·0008) risk of incident diabetes (table III).

In another model that included the baseline blood glucose and serum fructosamine concentrations as additional variables, a low lipid standardised vitamin E (below median) concentration was associated with a 5·1-fold (2·0-fold to 12·8-fold; P=0·0006) risk of incident diabetes. In an identical model in which dichotomised vitamin E was replaced by uncategorical lipid standardised vitamin E the association was also significant (P=0·0022). In another model, in which lipid standardised vitamin E concentration was replaced by unstandardised vitamin E concentration and serum low density lipoprotein cholesterol and triglyceride concentrations, plasma vitamin E had, if anything, a stronger association with the risk of diabetes (22% increment in risk per 1 μmol/l decrement in plasma vitamin E; P=0·0004). The addition (including maximal oxygen uptake, alcohol intake, systolic blood pressure, and serum high density lipoprotein cholesterol concentration) or depletion of any variable tested did not substantially weaken the association between low vitamin E concentration and diabetes risk. The relation between a low vitamin E concentration and increased risk of diabetes was significant in all models. When added to the model in table III neither family history of diabetes nor the ratio of waist to hip circumference had any residual association with diabetes risk.

All analyses were also repeated by using another definition of incident diabetes. Subjects diagnosed as diabetic but who had only dietary treatment were not included in the incident diabetic group. This reduced the number of subjects who became diabetic during follow up from 45 to 38. The relative risk for lipid standardised vitamin E concentration below median was then 3·3 (95% confidence interval 1·4 to 7·7; P=0·0057) in a logistic model with the same six variables as in table III. With the inclusion of blood glucose and serum fructosamine concentrations in the model the relative risk for lipid standardised vitamin E below median was 4·5 (1·6 to 12·8; P=0·0045).

Discussion

We found a strong independent association between low vitamin E status before follow up and an excess risk of diabetes in a cohort of almost 1000 randomly sampled men in eastern Finland. This observation supports the theory that free radical stress has a role in non-insulin dependent diabetes mellitus. The strength of the association is remarkable and militates against a chance finding. Our cohort was too small to allow tests of the dose-response relation and effect modifiers. However, any reasonable possibility of confounding was excluded statistically by adjustment for the main known risk factors for non-insulin dependent diabetes, such as obesity and other predictors of diabetes in the cohort.

The prevalence of non-insulin dependent diabetes mellitus is high in Finland[25] and has increased in the past few decades.[26] The mean plasma concentrations of the main dietary antioxidants, vitamins C and E, are low in men in eastern Finland.[27] The mean plasma vitamin E concentration in our cohort was 19 μmol/l. Mean plasma concentrations of between 24 and 28 μmol/l have been reported from continental Europe.[28] Also the dietary intake of vitamin E was low (mean 10 mg daily). In 566 (60%) men the vitamin E intake was below the recommended 10 mg daily.[29] Use of antioxidant supplements was rare. Only 12 men (1·3%) reported using any vitamin E product.

An important question is whether a low vitamin E concentration preceded the onset of diabetes and thus acted in its causation or whether the low concentration was a consequence of latent diabetes at the time of the baseline examination. We addressed this issue statistically by adjusting for measures of glucose metabolism at baseline. Besides fasting blood glucose concentration, the serum concentration of glycosylated protein as measured by fructosamine value was available. If the baseline vitamin E concentration had been influenced by a latent and unmanifested diabetes the control for glucose status at baseline should have eliminated this effect—certainly to the extent to which the validity and precision of these measurements allowed.

Our findings should be retested in other cohort studies with repetitive measurements of fasting blood glucose concentrations and possibly blood glucose concentrations after loading. Also randomised trials of vitamin E should include repeated measurements of blood glucose status to test whether the incidence of non-insulin dependent diabetes mellitus can be reduced by vitamin E supplementation. If our results are confirmed in other studies they will support the importance of free radical mechanisms in diabetes and suggest that a high vitamin E diet and vitamin E supplementation would be useful in the primary prevention of non-insulin dependent diabetes mellitus.

In a small randomised double blind crossover trial in 15 non-insulin dependent diabetic and 10 healthy subjects supplementation with 900 mg vitamin E daily for four months reduced oxidative stress and improved insulin action in a euglycaemic hyperinsulinaemic glucose clamp.[15,16] Vitamin E reduced the area under the curve and increased the total body glucose disposal and non-oxidative glucose metabolism in both healthy and diabetic subjects.

We can speculate that though susceptibility to non-insulin dependent diabetes mellitus is to a large extent determined genetically, manifestation of the disease may be more influenced by exogenous factors such as obesity. Golay and Felber have suggested that the resistance of peripheral tissues to glucose uptake is a consequence of permanently high lipid oxidation.[30] On the other hand, the oxidation of lipids could be enhanced if the concentrations of lipid soluble antioxidants such as vitamin E are low. The finding that vitamin E supplementation improved insulin sensi-

Key messages

- The manifestation of non-insulin dependent diabetes mellitus is influenced both by genes and by exogenous factors such as obesity
- Theoretically, free radical stress may have a role in diabetes
- In this study low vitamin E status was associated with an increased risk of diabetes
- The effect of antioxidants in preventing diabetes should be tested in clinical trials

tivity[15] supports this. To what extent vitamin E and possibly other antioxidants participate in the regulation of energy metabolism in muscle cells is an important basic research question.

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Conflict of interest: None.

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A randomised trial of three methods of giving information about prenatal testing

J G Thornton, J Hewison, R J Lilford, A Vail

Abstract

***Objective*—To test the effect of extra non-directive information about prenatal testing, given individually or in a class.**

***Setting*—Antenatal clinics in a district general hospital and a university hospital.**

***Design*—Randomised controlled trial; participants allocated to control group or offer of extra information individually or in class.**

***Subjects*—1691 women booking antenatal care before 15 weeks' gestation.**

***Interventions*—All participants received the usual information about prenatal tests from hospital staff. Individual participants were offered a separate session with a research midwife in which prenatal screening was described in detail. Class participants were offered the same extra information in an early prenatal class.**

***Main outcome measures*—Attendance at extra information sessions; uptake rates of prenatal tests; levels of anxiety, understanding, and satisfaction with decisions.**

***Results*—Attendance at classes was lower than at individual sessions (adjusted odds ratio 0·45; 95% confidence interval 0·35 to 0·58). Ultrasonography was almost universally accepted (99%) and was not affected by either intervention. Uptake of cystic fibrosis testing, high in controls (79%), was lowered in the individual group (0·44; 0·20 to 0·97) and classes (0·39; 0·18 to 0·86). Uptake of screening for Down's syndrome, already low (34%) in controls, was not further depressed by extra information in classes (0·99; 0·70 to 1·39) and was slightly higher in the individual group (1·45; 1·04 to 2·02). Women offered extra information had improved understanding and were more satisfied with information received; satisfaction with decisions about prenatal testing was unchanged. The offer of individual information reduced anxiety later in pregnancy.**

***Conclusions*—Ultrasonography is valued for non-medical reasons and chosen even by fully informed people who eschew prenatal diagnosis. The offer of extra information has no overall adverse effects on anxiety and reduces uptake of blood tests when background uptake rate is high (but not when it is already low). High uptake of prenatal blood tests suggests compliant behaviour and need for more information.**

Institute of Epidemiology and Health Services Research, Leeds University, Leeds LS2 9LN
J G Thornton, *reader in obstetrics and gynaecology*
R J Lilford, *director*
A Vail, *statistician*

Department of Psychology, Leeds University
J Hewison, *senior lecturer in psychology*

Correspondence to:
Dr Thornton.

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Introduction

Parents need information to make choices about prenatal screening tests in pregnancy,[1] but it is not clear how this should be delivered and how much information is optimal.[2-7] Antenatal clinic staff often give little information about prenatal screening,[8]